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(54) Title: AGENT FOR MEDICAMENTOUS TREATMENT OF ACUTE AND CHRONIC PAIN

(57) Abstract: The invention relates to an agent for the medicamentous treatment of acute and chronic pain, in particular of allodynia and hyperalgesia. Fields of application of the invention are medice and the pharmaceutical industry. A new pharmaceutical composition for the treatment of acute and/or chronic pain, in particular allodynia and hyperalgesia is provided, the pharmaceutical composition comprising calcium channel blockers which are suitable for blocking voltage-dependent calcium channels, in particular of the T-type, more preferably the CaV3.2 channel and/or of the L-type. Mibepradil and dihydropyridines can, for instance, be used as calcium channel blockers.

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Agent for medicamentous treatment of acute and chronic pain

The invention relates to an agent for medicamentous treatment of acute and chronic pain, in particular of allodynia and hyperalgesia.

This invention can be applied in the fields of medicine and pharmaceutical industry.

Mechanical stimuli of different subjective sensation are perceived through the skin, which is the largest sense organ in humans. The perception of sensation ranges from soft contact, pressure and tickle to perceptions of pain due to strong mechanical impact.

Pain conditions that are triggered by a stimulus that, under normal conditions, does not cause any pain, are called allodynic. Prominent examples thereof are a hypersensitivity of the skin due to a sunburn, an inflammation or a trauma. In order to distinguish it from hyperalgesia, it is important to note that allodynia is always connected with a change in the sensory modality. In other words, in the case of allodynia, it is, for instance, no longer possible to differentiate between the sensation modalities of a "soft touch" and "pain", or, in other words, that a stimulus which is normally not painful causes pain. This means that there is a loss in the specificity of the sensory modalities. In contrast, in the case of hyperalgesia, the quality of the sensory sensation has not changed. A touch is still perceived as a touch and pain is still perceived as pain. One, however, is more sensitive and quantitatively feels a more intensive touch or pain. The transition from allodynia to hyperalgesia, however, is mostly gradual. It is at present assumed that both the peripheral and the central sensitisation of the pain system contribute to the two pathological conditions (Julius D. Basbaum Al. (2001) Molecular mechanisms of nociception. Nature 2001 413(6852):203-10; Textbook of Pain, (1999) ed. Wall PD and Melzack R. Philadelphia, Pa, WB Saunders, ISBN 0-443-06252-8).

Neuropathic pain, such as hyperalgesia and allodynia both occur as symptoms of many different and varied diseases and injuries (Epidemiology of Pain (1999), IASP Press, Editors: Ian K. Crombie, Peter R. Croft, Steven J. Linton, Linda LeResche,

Michael von Korffm, ISBN 0-931092-25-6). Examples thereof include syndromes such as rheumatoid arthritis, cancer pain, sport injuries, chronic and acute back pain, herpes zoster and post-surgical pain requiring intensive treatment. The treatment of neuropathic pain is often very difficult because of the multiple underlying mechanisms that are poorly understood. Any novel analgetic target has a great therapeutic potential.

Allodynia is a pathological condition in which the person perceives soft mechanical stimuli on the skin as pain, which, under normal conditions, are merely perceived as a soft contact or tickling. This is probably due to a change in the connections in the spinal cord.

The different stimuli are registered by the endings of sensory neurons that are present in the spinal ganglion and the peripheral terminations of which extend to the ends of the extremities.

Due to the requirements as to the processing of different mechanical stimuli, this group of neurons has a very heterogeneous population. They differ from each other in terms of the conduction velocity of their axons, the cell size, the threshold for mechanical generation of stimulation and their adaptation behaviour:

1. A- β fibres (more than 10 m/s): slowly adapting SA fibres and rapidly-adapting RA fibres (both tactile receptors)
2. A-delta fibres (1-10 m/s): AM fibres (nociceptor) and D-hair mechanoreceptors (highly sensitive tactile receptors)
3. C-fibres (under 1 m/s) (nociceptors)

Johnson (Kenneth O. Johnson, 2001, The roles and functions of cutaneous mechanoreceptors, Current opinion in neurobiology, 11;455-461, for mouse: Koltzenburg M, Stucky CL, Lewin GR. Receptive properties of mouse sensory neurons innervating hairy skin. J Neurophysiol. 1997 Oct;78(4):1841-50) summarises the cutaneous mechanoreceptors in humans.

Currently, two classes of pharmaceuticals are used for treating allodynia and hyperalgesia, namely the class of non-steroidal anti-inflammatory drugs (NSAID) (such as indomethacin and aspirin) and the opiates. The latter have an effect on the central nervous system and they can only be applied to a limited extent due to the known side-effects such as dependency and tolerance. The NSAIDs are effective in the periphery and are therefore safer and more effective in many cases.

In chronic conditions such as rheumatoid arthritis, however, NSAIDs have not turned out to be effective so that further targets for nociceptive treatment have to be found. In this way, on the one hand, it would be possible to develop agents that are more effective than the NSAIDs or, on the other hand, these classes of pharmaceuticals could be supplemented due to their different mode of activity and they could mutually potentiate their analgesic effect.

Thus, the technical problem underlying the invention is to develop a new agent for the medicamentous treatment of acute and chronic pain, in particular of allodynia and hyperalgesia.

This technical problem is solved according to the claims.

According to the present invention, it was surprisingly found that voltage-dependent calcium channels are involved in the transduction of mechanical stimuli by nociceptive/non-nociceptive neurons. As a consequence, a blockade of the mechanical sensitivity of the skin by means of calcium channel blockers such as mibepradil or a dihydropyridine derivative is the basis of the invention and thus offers a totally new treatment of pain such as allodynia and hyperalgesia.

A new pharmaceutical composition for the treatment of acute and/or chronic pain, in particular allodynia and hyperalgesia is provided for, comprising calcium channel blockers which are suitable for blocking voltage-dependent calcium channels, in particular of the T-type, most preferably the CaV3.2 channel, and/or of the L-type. Mibepradil and dihydropyridine are preferred calcium channel blockers to be used in accordance with the present invention.

Further calcium channel blockers including T-type channel blockers are known in the art. Such substances which can be used in accordance with the present invention include 1,4-dihydropyridine derivatives as disclosed in WO98/31680, EP0164588 and EP0158211, succinimide derivatives like methylphenylsuccinimide, diphenylmethylpiperazine derivatives like 7-[4-[bis(4-fluorophenyl)-methyl]-1-piperazinyl]methyl]-2-[2-hydroxyethyl]amino]-4-(1-methylethyl)-2,4,6-cycloheptatrien-1-one (U92032; Pharmacia and Upjohn), flunarizine, efonidipine, pimozone, zonisamide, depacon, amiloride and/or valproic acid.

The agent of the invention can, amongst others, be used in the treatment of pain associated with rheumatoid arthritis, the formation and growth of tumours, injuries, back pain, herpes zoster and post-surgical pain.

The agent can be applied in local, oral, parenteral, inhalative or intranasal form, in any pharmaceutically acceptable form. In accordance with a preferred embodiment of the invention, the calcium channel blocker is mibepradil (see Figure 3), its pharmaceutically acceptable analogues, salts and esters or dihydropyridines, such as diazepin, as well as their pharmaceutically acceptable analogues (see Figure 4). In another embodiment of the invention, for extending the possibilities of therapy, ointments, gels or creams and solutions or suspensions are used as local forms of application. The pharmaceutical composition of the invention can furthermore be included into a tape or can be applied in form of a spray, in particular a nasal spray.

Another advantage of the invention is that it can be applied for the systemic treatment of pain. For extending the possibilities of therapy, tablets, capsules, coated tables, granulates, effervescent tablets, juice, syrup, suspensions or solutions can be used as oral forms of application. In this case, the drug form used is formed of biologically utilizable or biodegradable substances, wherein the biological materials are proteins or proteides, lipids or lipoids, carbohydrates or polysaccharides or mixtures of several of such materials.

For extending the possibilities of therapy, in addition, to the pharmaceutical composition of the invention, at least one other analgetic, preferably of the NSAID class can be used. In this way, it is possible to supplement the different biophases and to enhance the analgetic effect.

Preferably, the concentration of mibepradil is between 1 and 10 µM, more preferably 3 to 7 and most preferably 5 µM.

Examples

The invention described is now explained in more detail by way of the following examples. The person skilled in the art can take various other embodiments from the present description. Attention, however, is drawn to the fact that the examples and the description are merely intended to explain and not to limit the invention.

Analysis of the occurrence and influence of voltage-dependent calcium channels in D-hair mechanoreceptors

With regard to the research of pain, amongst the various kinds of mechanoreceptors, in particular the so-called D-hair mechanoreceptors which are an excellent example of tactile receptors thanks to their high sensitivity. Stucky et al. found that in mice which lacked the gene for the neurotrophin NT-4 a loss of D-hair mechanoreceptors occurs (Stucky CL, DeChiara T, Lindsay RM, Yancopoulos GD, Koltzenburg M., Neutrotrophin 4 is required for the survival of a subclass of hair follicle receptors. J. Neurosci. 1998 Sep 1;18(17):7040-6). In the present invention, these mice were used for the detection of genes which are specifically expressed in D-hair and could therefore be important for their function. For this purpose, the gene expression of WT and NT-4 ko (knock-out) mice were analysed in a comparison to detect genes that were under-regulated in NT-4 ko mice. As, with regard to the skin sensory system, the only difference between WT and NT-4 ko mice is the loss of D-hair, these under-regulated genes were potential candidates for D-hair specific genes. A combination of gene chip analysis and DNA subtraction methods were used for expression studies.

A combined analysis of the gene chip expression data and the DNA subtraction data resulted in 29 genes which are most probably under-regulated in NT-4 ko mice. For detecting genes which are specifically expressed in a subtype of the spinal neurons, their expression pattern in the spinal ganglion was analysed. For this purpose, in-situ hybridisations with Dig labelled cRNA were carried out. D-hair specific genes should have been expressed in medium-size neurons and under-regulated in NT-4 ko mice.

All genes were expressed in a neuronal manner. Two genes fulfilled the above-mentioned criteria for D-hair specificity. These were the genes TrkB and T-type calcium channel CaV3.2. (Figures 1 and 2)

TrkB ist the cellular receptor of NT-4 and BDNF and therefore an under-regulation of TrkB in NT-4 mice could be expected and confirmed the usefulness of the present experimental approach. The findings, however, that CaV3.2 is specifically expressed in D-hair mechanoreceptors is new and surprising as it has so far been unknown that calcium channels are involved in mechanosensation.

Although T-type calcium currents have already been identified in the eighties by means of electrophysiological studies with chick sensory neurons (Fox AP, Nowycky MC, Tsine RW, Kinetic and pharmacological properties distinguishing three types of calcium currents in chick sensory neurons. J Physiol. 1987 Dec;394:149-72), the genes were cloned only recently. The T-type subtype CaV3.2 consists of 2042 amino acids and was originally cloned in heart (therefore, its alternative name alpha1H) (Cribbs LL, Lee JH, Yang J, Satin J, Zhang Y, Daud A, Barclay J, Williamson MP, Fox M, Rees M, Perez-Reyes E. Cloning and characterization of alpha1H from human heart, a member of the T-type Ca²⁺ channel gene family. Circ. Res. 1998 Jul 13;83(1):103-9), but was later on also detected in kidney and liver, and, to a smaller extent, also in brain. The expression studies underlying the present invention showed that CaV3.2 is expressed very specifically in medium-size spinal ganglion cells. In the spinal ganglion, there are two kinds of medium-size neurons, the AM- and D-hair mechanoreceptors. Due to the findings obtained by the present invention, i.e. that, parallel to the loss of D-hair, also CaV3.2 positive neurons disappear in NT-4 ko mice, it is obvious that CaV3.2 is specifically expressed in D-hair.

The logical question was which role said calcium channel plays in D-hair mechanoreceptors and whether it is indispensable for their function. For these studies, two known calcium channel blockers, i.e. mibepradil and nickel, were used (Martin RL, Lee JH, Cribbs LL, Perez-Reyes E, Hanck DA, Mibepradil block of cloned T-type calcium channels. J. Pharmacol Exp Ther. 2000 Oct;295(1):302-8 (Lee JH, Gomora JC, Cribbs LL, Perez-Reyes E. Nickel block of three cloned T-type calcium channels: low concentrations selectively block alpha1H. Biophys J. 1999 Dec;77(6):3034-42). Mibepradil (see Figure 3) is a non-dihydropyridine calcium channel antagonist that has a relatively high selectivity for T-type calcium channels. Until a few years ago, mibepradil was used for the alternative treatment of hypertension and angina pectoris (Frishman WH, Mibepradil: A New selective T-Channel Calcium Antagonist for Hypertension and Angina Pectoris. J Cardiovasc Pharmacol Ther. 1997 Oct;2(4):321-330) (Brogden RN, Markham A.: Mibepradil. A

review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the management of hypertension and angina pectoris. Drugs. 1997 Nov;54(5):774-93. Review), but it was removed from the market due to its severe interaction with other medicaments (Clozel JP, Ertel EA, Ertel SI; Voltage-gated T-type Ca²⁺ channels and heart failure. Proc Assoc Am Physicians. 1999 Sep-Oct;111(5):429-37. Review). The EC₅₀ of mibepradil on cells is between 0.1 and 1 µM, depending on the cell system (Martin et al., 2000, see above). Mibepradil however has an almost identical effect on both T-type isotypes CaV3.1 und CaV3.3. The other blocker nickel has a 70 times higher EC₅₀ on CaV3.2 than on the other isotypes (approx. 10 µM on CaV3.2 and 216 µM CaV3.3 and 250 µM on CaV3.3). Nickel, however, is cytotoxic so that it is only restrictedly suitable for pharmacologic analyses of living tissue and is even unsuitable for medicamentous use.

The use of the skin-nerve preparation, which the present invention is based on, allows for the electrophysiological analysis of the different neurofibre types which innervate the skin (Koltzenburg et al., 1997, see above). The saphenous nerve and the region of the skin that it innervates are prepared from freshly killed mice and are mounted in a bath of physiological buffer. After mechanical or electrical stimulation of the skin, the nerve signals can be received directly from the nerve. For determining the effective concentration, tests were carried out with different concentrations of mibepradil in the bath solution. The EC₅₀ of mibepradil on cells is between 0.1 and 1 µM. At high concentrations of more than 25 µM mibepradil in the bath solution, there was an almost complete and unspecific blocking of the mechanical sensitivity. If the concentration was lowered to 3 µM, D-hair mechanoreceptors and, in part, also AM mechanoreceptors are specifically inhibited, the A-β fibres, however, not. The unspecific blockade at high concentrations may be due to the fact that mibepradil, at high concentrations, has a very unspecific effect on other ubiquitously expressed calcium channels. Such blocking is lost at lower concentrations. The blocking of some AM mechanoreceptors also at low concentrations of mibepradil could have two reasons. The first possibility is that AM mechanoreceptors, too, express CaV3.2. This, however, is not very likely based on the findings obtained by the in-situ hybridisation within the framework of the present invention. It may rather be assumed that a different isotype, i.e. CaV3.3 is expressed in AM mechanoreceptors. It was not possible to detect CaV3.3 in in-situ hybridisation experiments in spinal ganglia, but other groups reported the expression of this calcium channel in medium-size cells. And it has been known that the semi-

effective concentration of mibepradil on CaV3.3 is almost identical to the one on CaV3.2. To sum up, it is concluded that the calcium channel CaV3.2 in spinal ganglia specifically expresses in D-hair mechanoreceptors and is therefore indispensable for its function. The discovery that the voltage-dependent calcium channels are involved in the transduction of mechanical stimuli by nociceptive and non-nociceptive neurons is new. Due to their physiological properties together with their specific localisation on the site of the mechanotransduction in the periphery, the calcium channels are ideal targets for pain therapy, which the invention is based on.

Functional model

It is not very likely that this T-type calcium channel is the mechanosensitive ion channel that is responsible for the generation of the receptor potential. It is rather concluded that this calcium channel is a kind of signal enhancer. Moderately strong depolarisations which are triggered by soft mechanical stimuli do normally not surpass the threshold for the initiation of an action potential. It would be possible to achieve a signal enhancement by inserting an ion channel which is activated even at low voltages. This would be a simple explanation for the high sensitivity of D-hair mechanoreceptors. CaV3.2 has ideal prerequisites for fulfilling such a task as it is activated even at low voltages. Another feature of the D-hair receptors is their fast adaptation, i.e. they are only active at the beginning and at the end of a mechanical stimulus, i.e. they are acceleration receptors. A property of the CaV3.2 receptor is that it deactivates if these are stimuli in rapid succession, which is well compatible with the fast-adapting property of D-hair receptors.

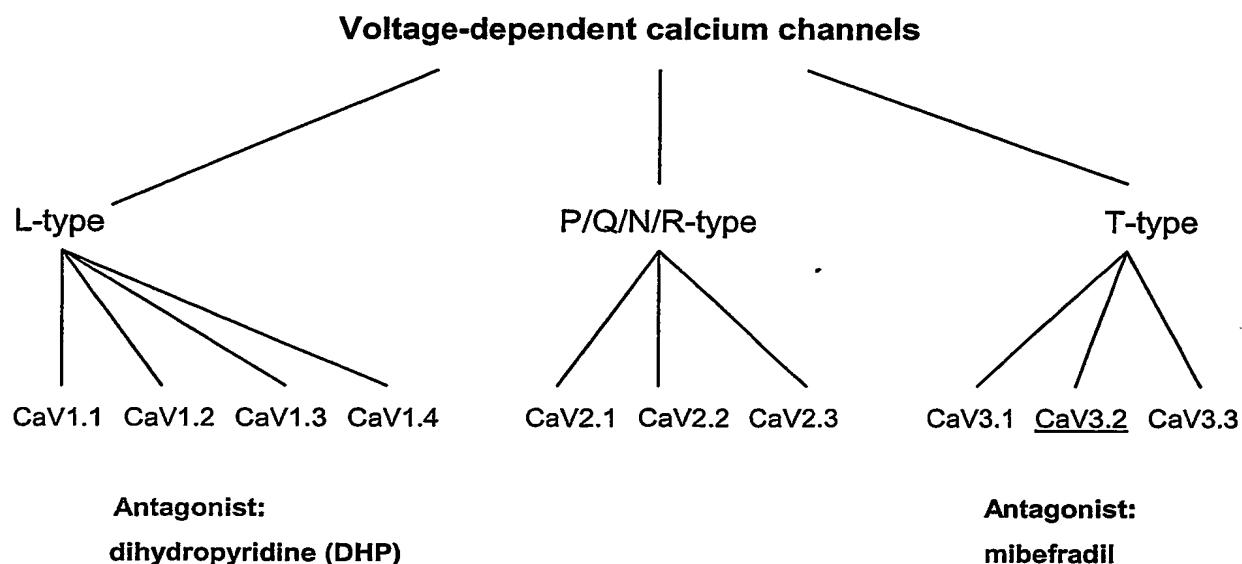
Therapeutic approach

The experiments of the invention were carried out on mice. Human CaV3.2 shows a very high genetic homology and is very likely to exert similar functions. The new findings that the use of a calcium channel blocker (e.g. with mibepradil even at low concentrations (25 µM or less)) virtually inhibits the entire cutaneous mechanotransduction, is of particular significance in the treatment of allodynia. These are pathological conditions in which the person perceives soft mechanical stimuli on the skin, which are normally merely perceived as soft touch or tickling, as pain. This is most probably due to a change in the neuronal connections in the spinal cord.

A blockade of the mechanical sensitivity of the skin by the systemic or topical addition of calcium channel blockers such as mibepradil is of great clinical significance in terms of the treatment of such conditions.

Extension of the possibilities of application

The data of the invention primarily relate to the calcium channel CaV3.2, a sub-type of the voltage-dependent calcium channels. It should, however, be noted that the blockade of other voltage-dependent calcium channels can also be used for the treatment of the cited pain. It has been found that the use of higher concentrations of mibepradil resulted in the complex blocking of other mechanoreceptors which have other calcium channels. The group of voltage-dependent calcium channels can be classified as follows:



As a result, at higher concentrations, mibepradil blocks not only the D-hair mechanotransduction but also the entire mechanotransduction. This is probably due to a blocking of other voltage-dependent calcium channels, in particular the L- and N-type. N-type calcium channels are expressed in all sensory neurons, whereas the L-type is mainly expressed in small cells (Scroggs RS, Fox AP; Calcium current variation between acutely isolated adult rat dorsal root ganglion neurons of different size. J. Physiol. 1992 Jan;445:639-58) and are blocked by mibepradil at higher concentrations (about 10-fold higher than necessary for T-type blocking) (Mehrke G, Zong XG, Flockerzi V, Hofmann F. The Ca(++)-channel

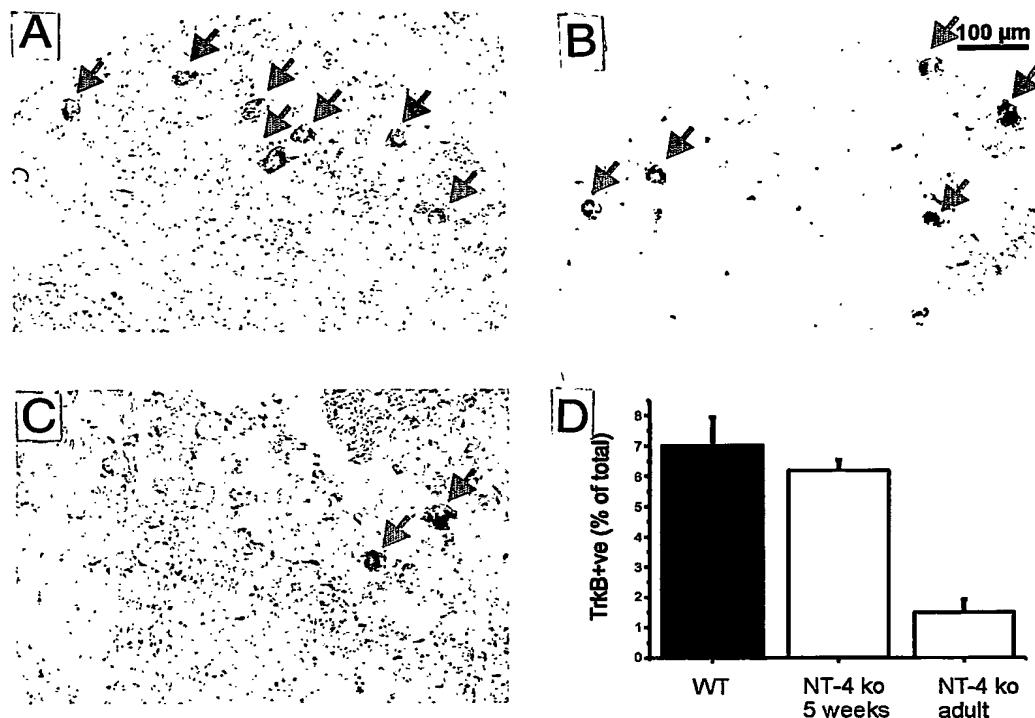
blocker Ro 40-5967 blocks different T-type and L-type Ca⁺⁺ channels. J Pharmacol Exp Ther. 1994 Dec;271(3):1483-8). This is why also dihydropyridines, the more effective L-type blockers, can be used for the treatment of the mentioned conditions of pain. Dihydropyridines have already been used clinically, e.g. for the treatment of hypertension (Reuter H, Porzig H, Kokubun S, Prod'hom B.; Calcium channels in the heart. Properties and modulation by dihydropyridine enantiomers. Ann N Y Acad Sci. 1988;522:16-24. Review).

Claims:

1. Pharmaceutical composition for the treatment of acute and/or chronic pain comprising calcium channel blockers which are capable of blocking voltage-dependent calcium channels.
2. Pharmaceutical composition as defined in claim 1 wherein the calcium channel is a T-type or L-type channel.
3. Pharmaceutical composition as defined in claim 1 or 2 for the treatment of allodynia or hyperalgesia.
4. Pharmaceutical composition according to any one of claims 1 to 3 wherein the calcium channel blocker is mibepradil, its pharmaceutically acceptable analogues, salts or esters or a dihydropyridine.
5. Pharmaceutical composition for the treatment of pain associated with rheumatoid arthritis, cancer, injuries, back pain, herpes zoster and post-operative pain.
6. Pharmaceutical composition according to any one of claims 1 to 5 for the topical, oral, parenteral, inhalative or intranasal administration.
7. Pharmaceutical composition according to claim 6 in form of an ointment, gel, crème or a solution or suspension, or plaster.
8. Pharmaceutical composition according to claim 6 in form of a nasal spray or inhalator.
9. Pharmaceutical composition according to any one of claims 1 to 3 for the systemic therapy of pain.
10. Pharmaceutical composition according to any one of claims 1 to 3 characterised in that tablets, capsules, coated tablets, granulates, juice, syrup, suspensions or solutions are used as oral forms of application.
11. Pharmaceutical composition according to any one of claims 1 to 3 characterised in that the drug form used is formed of biologically utilizable or

biodegradable substances wherein the biological materials are proteins or proteides, lipids or lipoids, carbohydrates or polysaccharides or mixtures of several of such materials.

12. Pharmaceutical composition according to any one of claims 1 to 3 characterised in that additionally one other pain killer is used.
13. Pharmaceutical composition according to claim 12 characterised in that the pain killer used in combination is an NSAID, a 5HT_{1D} agonist, a dopamin D₂ receptor antagonist, a secale alcaloid, a beta blocker, a calcium channel blocker or a neurokinin antagonist.
14. Pharmaceutical composition according to claim 12 characterised in that the NSAID is ibuprofen, meoxicam, indomethacin or naproxen.
15. Pharmaceutical composition according to claim 12 characterised in that the 5HT_{1D} agonist is sumatriptan, MK-452, naratriptan or 311C.
16. Pharmaceutical composition according to claim 12 characterised in that the dopamin D₂ receptor antagonist is metoclopramid.
17. Pharmaceutical composition according to claim 12 characterised in that the secale alcaloid is ergotamin, dihydroergotamin or metergolin.
18. Pharmaceutical composition according to claim 12 characterised in that the beta blocker is propranolol or metoprolol.
19. Pharmaceutical composition according to claim 12 characterised in that the calcium channel blocker is flunarizin or lomerizin.
20. Pharmaceutical composition according to claim 12 characterised in that the pain killer to be administered in combination is acetylsalicylic acid, paracetamol, clonidin, methysergid, dotarizin, lisurid, pizotifen, valproat, aminotriptilin CP-122,288 or UK 116,044.



The figure shows the cellular expression of TrkB mRNA in the dorsal root ganglion

- A: TrkB positive cells (marked with arrows) in the WT
- B: TrkB positive cells in young (4 weeks old) NT4 knockout mice
- C: TrkB positive cells in adult (12 weeks old) NT4 knockout mice
- D: Quantification of the TrkB positive cells

Fig.1

CaV3.2 Expression

NT4 Wildtype

NT4 KO

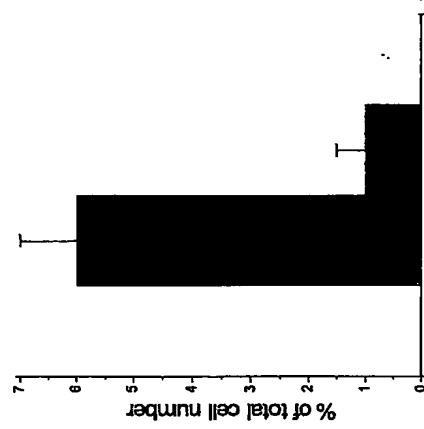
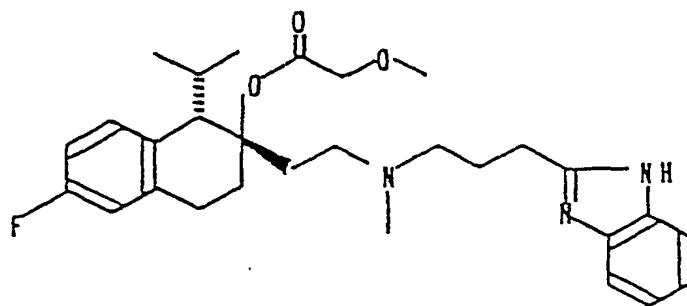


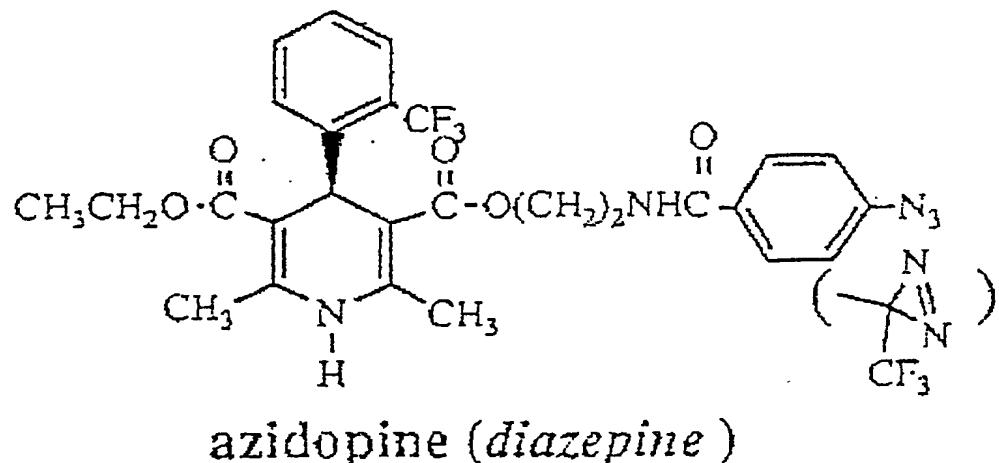
Fig. 2 The in-situ hybridization shows the cellular localization of Cav3.2 mRNA in the dorsal root ganglion. In the Wildtype, CaV3.2 is expressed in approximately 6% of the cells (middle size), and in the NT4 knockout mice, the number of the CaV3.2 positive cells is reduced to approximately 1%. This is a clear indication that Cav3.2 is specifically expressed in D-hair mechanoreceptors.



(1*S*,2*S*)-2-[2-[(3-(2-Benzimidazolyl)propyl)methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthyl methoxyacetate dihydrochloride

Mibefradil

Fig. 3



azidopine (*diazepine*)

Fig. 4

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WO 2004/000311 A3

(54) Title: **PHARMACEUTICAL COMPOSITION COMPRISING CALCIUM CHANNEL BLOCKERS FOR THE TREATMENT OF PAIN**

(57) Abstract: The invention relates to an agent for the medicamentous treatment of acute and chronic pain, in particular of allodynia and hyperalgesia. Fields of application of the invention are medicine and the pharmaceutical industry. A new pharmaceutical composition for the treatment of acute and/or chronic pain, in particular allodynia and hyperalgesia provided, the pharmaceutical composition comprising calcium channel blockers which are suitable for blocking voltage-dependent calcium channels, in particular of the T-type, more preferably the CaV3.2 channel and/or of the L-type. Mibepradil and dihydropyridines can, for instance, be used as calcium channel blockers.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/06551

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/4184 A61K31/4422 A61K45/06 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, PASCAL, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRAYENBUHL J C ET AL: "Drug-drug interactions of new active substances: Mibepradil example" EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, vol. 55, no. 8, October 1999 (1999-10), pages 559-565, XP001153272 ISSN: 0031-6970 the whole document	1-12
X	US 6 358 706 B1 (ZHU JESSICA Y ET AL) 19 March 2002 (2002-03-19) column 4, line 7 - line 11 column 5, line 24 - line 39	1-12 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the International search

13 November 2003

Date of mailing of the International search report

12 03 2004

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 03/06551

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DOGRUL A ET AL: "L-type and T-type calcium channel blockade potentiate the analgesic effects of morphine and selective 'mu' opioid agonist, but not to selective 'delta' and 'kappa' agonist at the level of the spinal cord in mice" PAIN 2001 NETHERLANDS, vol. 93, no. 1, 2001, pages 61-68, XP001153273 ISSN: 0304-3959 abstract 'Discussion' -----	1-12
X	US 5 929 122 A (REIMANN WOLFGANG) 27 July 1999 (1999-07-27) column 1, line 21 - line 67 column 2, line 31 - column 3, line 18 claims -----	1-12
P,X	EP 1 312 362 A (KOREA INST SCIENCE TECHNOLOGY) 21 May 2003 (2003-05-21) the whole document -----	1-12
A	MUTH J N ET AL: "Use of transgenic mice to study voltage-dependent Cachannels" TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER TRENDS JOURNAL, CAMBRIDGE, GB, vol. 22, no. 10, 1 October 2001 (2001-10-01), pages 526-532, XP004307622 ISSN: 0165-6147 the whole document -----	
A	ANGUS J A ET AL: "Targetting voltage-gated calcium channels in cardiovascular therapy" LANCET, XX, XX, vol. 356, no. 9238, 14 October 2000 (2000-10-14), pages 1287-1289, XP004264172 ISSN: 0140-6736 the whole document -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/06551

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-11

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: -

The subject-matter of present claim 1 (and the dependent claims 2, 3 and 5-11) is defined by means of the functional feature 'calcium channel blockers which are capable of blocking voltage-dependent calcium channels'.

Because of the character of the functional feature, it cannot be guaranteed that the performed search is complete.

It cannot be excluded that compounds fulfilling the requirements of the functional feature have not been identified as doing so in the prior art.

If such compounds have not been identified in the application either, they have not been covered by the search.

Furthermore, the definition 'dihydropyridine' (claim 4) does not fulfil the requirements of Art. 5 and 6 PCT. It is unclear which compounds are encompassed by the above definition. The claim so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. The same applies to the definitions 'analogues' and 'esters' (claim 4).

The search has been carried out, based on the functional feature per se as well as the examples given in the application, the compounds defined in claim 3 as well as the compounds, partly defined by reference to other documents, mentioned on p. 3, last paragraph.

It is further pointed out that the substantive examination can only be carried out to the same extent as the search.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5),

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/06551

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 6358706	B1	19-03-2002	AU CA EP JP TR WO	7871600 A 2389031 A1 1224218 A1 2003529337 T 200201119 T2 0130844 A1	08-05-2001 03-05-2001 24-07-2002 07-10-2003 21-11-2002 03-05-2001
US 5929122	A	27-07-1999	DE AT AU AU CA DE DK EP ES HK HU JP PT SI	19641576 C1 209485 T 726341 B2 3998497 A 2217846 A1 59705525 D1 835656 T3 0835656 A1 2168562 T3 1009400 A1 9701618 A2 10147520 A 835656 T 835656 T1	07-05-1998 15-12-2001 02-11-2000 23-04-1998 09-04-1998 10-01-2002 11-02-2002 15-04-1998 16-06-2002 20-09-2002 28-01-1999 02-06-1998 31-05-2002 31-08-2002
EP 1312362	A	21-05-2003	KR EP JP US	2003037081 A 1312362 A1 2003137813 A 2003086980 A1	12-05-2003 21-05-2003 14-05-2003 08-05-2003

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